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Immunopharmacology and inflammation

Eriodictyol attenuates cisplatin-induced kidney injury by inhibiting oxidative stress and inflammation

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ABSTRACT

Eriodictyol, a flavonoid present in citrus fruits, has been reported to have antioxidant and anti-inflammatory effects. In this study, the protective effects of eriodictyol on cisplatin (CP)-induced kidney injury were detected. CP-induced kidney injury model was established by administration of CP (20 mg/kg). The results showed that treatment of eriodictyol inhibited the production of blood urea nitrogen (BUN), creatinine, MDA, TBARS, reactive oxygen species (ROS), as well as the production of TNF-α, and IL-1β in kidney tissues induced by CP. Eriodictyol also up-regulated the activities of SOD, CAT, and GSH-PX decreased by CP. Furthermore, eriodictyol was found to up-regulate the expression of Nrf2/HO-1 and inhibited CP-induced NF-κB activation in kidney tissues. In conclusion, eriodictyol protected against CP-induced kidney injury through activating Nrf2 and inhibiting NF-κB activation.

1. Introduction

Nephrotoxicity is the major adverse effect of cisplatin (CP), a potent chemotherapeutic antitumor drug that often used in the treatment of malignant tumors (Launay-Vacher et al., 2008). Studies showed that CP was accumulated in kidney tissues more than other organs (Chirino and Pedraza-Chaverri, 2009). Entry of CP into tubular cells lead to oxidative stress and inflammatory response by inducing inflammatory and oxidant mediators TNF-α, IL-1β, and reactive oxygen species (ROS) release (Yao et al., 2007). Hence, treating aimed to inhibit oxidant stress and inflammation may provide benefit effects against CP-induced kidney injury (Chirino and Pedraza-Chaverri, 2009; Rodrigo and Bosco, 2006). Previous studies showed that many medicinal plants had the ability to inhibit oxidant and inflammatory response (Atessahin et al., 2005; Wongmekiat et al., 2011). And nowadays, much attenuation has been focused on natural anti-inflammatory drugs in medicinal plants in the treatment of CP-induced kidney injury (Ajith et al., 2007; İşeri et al., 2007).

Eriodictyol (Fig. 2A), a flavonoid present in citrus fruits, has been reported to have antioxidant and anti-inflammatory effects (Lee et al., 2007; Rossato et al., 2011). Previous studies showed that eriodictyol had the ability to protect endothelial cells against oxidative stress-induced cell death (Lee et al., 2015). Eriodictyol also attenuated β-amyloid peptide-induced oxidative cell death in neurons (Jing et al., 2015). Eriodictyol has been reported to attenuate retinal inflammation and plasma lipid peroxidation in early diabetic rats (Bucolo et al., 2012). Furthermore, eriodictyol was found to inhibit NO production in LPS-stimulated RAW264.7 cells (Dai et al., 2008). However, the protective effects and mechanism of eriodictyol against CP-induced kidney injury remain unclear. Therefore, the purpose of this study was to investigate the protective effects of eriodictyol against CP-induced kidney injury in mice.

2. Materials and methods

2.1. Reagents

Eriodictyol, Dimethyl sulfoxide (DMSO), and cisplatin were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Mouse TNF-α and IL-1β ELISA kits were obtained from R&D Systems (Minneapolis, MN). Antibodies against NF-κB, IκBα, Nrf2, HO-1, and β-actin were purchased from Santa Cruz Biotechnology (Autogen, Bioclear, UK). GSH-PX and SOD assay kits were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China).

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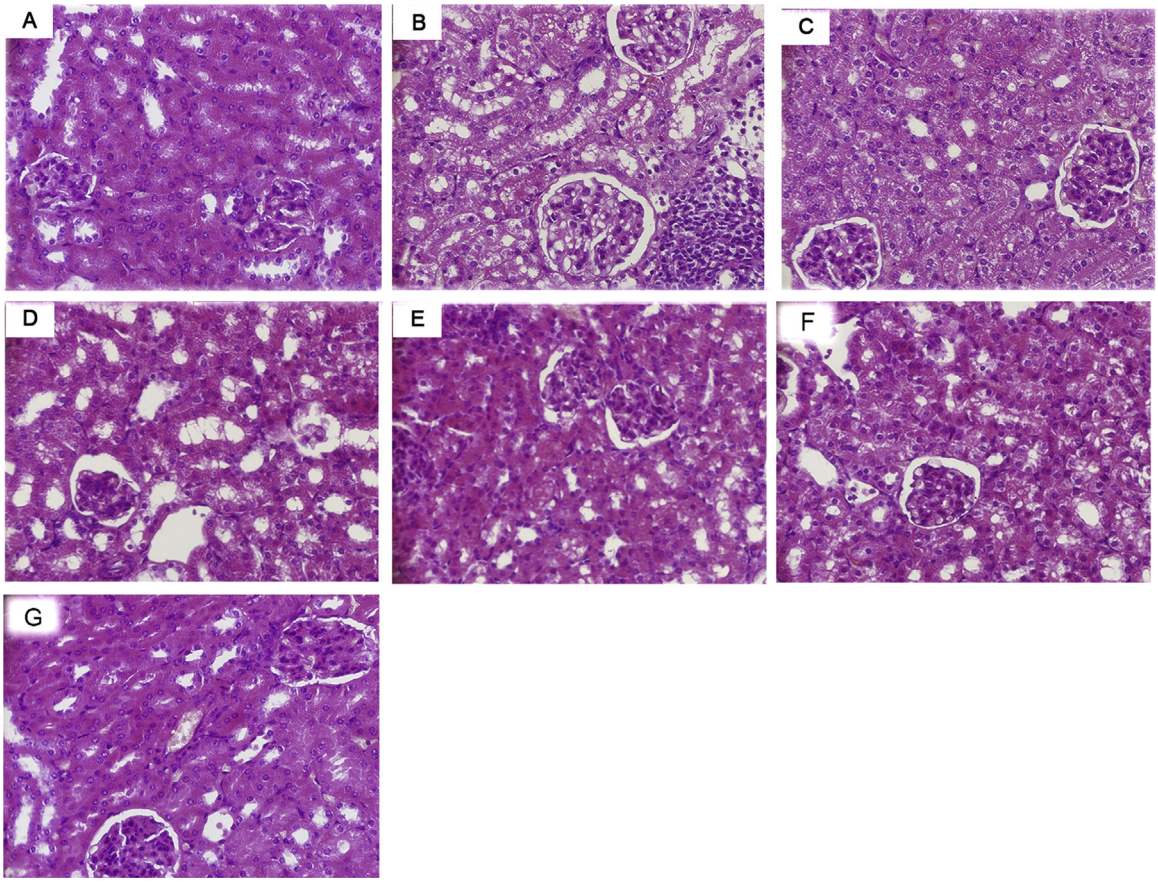

Fig. 1. Effects of eriodictyol on histopathological changes in kidney tissues in CP-induced kidney injury. Representative histological changes of kidney obtained from mice of different groups. A: Control group, B: CP group, C: eriodictyol (10 mg/kg)+CP group, D: eriodictyol (20 mg/kg) +CP group, E: eriodictyol (40 mg/kg)+CP group, F: CP+eriodictyol (40 mg/kg) group, G: eriodictyol (40 mg/kg) group (Hematoxylin and eosin staining, magnification 200 ×).

2.2. Animals

Male BALB/c mice, weighing approximately 18–22 g, were purchased from the Center of Experimental Animals of Dong-A University (Busan, Korea). The experiments were approved by the Dong-A University Animal Care and Use Committee. The mice were maintained in a controlled room with temperature (24 ± 1 °C) and humidity (40–80%). The mice were received food and water ad libitum.

2.3. Experimental protocols

Eighty-four mice were randomly divided into seven groups: normal control group, eriodictyol (40 mg/kg) treatment group, CP group, eriodictyol (10, 20, 40 mg/kg)+CP group, CP+eriodictyol (40 mg/kg) group. The mice of CP group were received CP (20 mg/kg) diluted with 5% DMSO (v/v) as a single intraperitoneal injection. The mice of eriodictyol (10, 20, 40 mg/kg)+CP group were received with eriodictyol intraperitoneally for three consecutive days. Then the mice were given CP (20 mg/kg). The mice of CP+eriodictyol (40 mg/kg) group were given CP (20 mg/kg) and then received with eriodictyol intraperitoneally for three consecutive days. The mice were killed four days after CP challenge.

2.4. Histologic analysis

The kidney tissues were fixed with 4% paraformaldehyde and embedded in paraffin. After deparaffinization and dehydration, the tissues were cut into 5 μm sections. The sections were observed by light microscopy.

2.5. Kidney function analysis

The blood was collected to obtain serum. Serum creatinine and BUN levels were detected by using an autoanalyzer according to the manufacturer's instructions.

2.6. GSH-PX, CAT, and SOD assay

The levels of SOD, CAT, and GSH-PX in kidney tissues were tested by SOD, CAT, and GSH-PX detection kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) according to the manufacturer's instructions.

2.7. MDA, TBARS, and ROS assay

The level of kidney MDA was measured by MDA test kit (Nanjing jiancheng Bioengineering Institute, Nanjing, China) according to the manufacturer's instructions. The level of ROS was measured based on the oxidation of DCFH-DA to DCF as described previously (Shinomol and Muralidhara, 2007). The level of TRARS was measured by the TBA as described previously (Hagar et al., 2015).

2.8. Cytokines assay

The production of inflammatory cytokines TNF-α and IL-1β in kidney tissues were measured by using ELISA kits (R&D Systems, Minneapolis, MN) according to the manufacturer's instructions.